Original Research Article

Is Serum Lactate a Good Predictor of Mortality in Children Aged 2 Months to 5 Years With Pneumonia in Central Vietnam

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Son Bui-Binh-Bao[1], Trang Nguyen-Thi-My[2], Anh Nguyen-Duy-Nam[1], Nguyen Thi Kim Hoa[3], and Dung Pham-Van[2]

Abstract

Pneumonia is a major cause of morbidity and mortality in children globally. Lactate, a product of anaerobic cellular metabolism, has been used as an indicator of poor tissue oxygenation and cellular hypoxia. Our objective was to determine whether serum lactate concentration at hospital admission predicted mortality in children aged 2 months to 5 years with pneumonia. Two hundred and eighty-one pediatric patients admitted to the Department of Pediatrics of a provincial hospital with WHO-defined pneumonia and severe pneumonia were included; of whom, 8 died during hospital stay. The median serum lactate concentration was 4.8 mmol/l (IQR 2.6-6.9) among children who died and 3.6 mmol/l (IQR 2.8-4.3) among children who survived ($P > .05$); 4.1 mmol/l (IQR 2.7-4.7) among children with severe pneumonia and 3.5 mmol/l (IQR 2.8-4.3) among children with pneumonia ($P > .05$). Serum lactate concentration had a low value in predicting pneumonia-related mortality (AUC 0.68, 95% CI 0.62-0.73); and the concentration cut-off of >4.06 mmol/l had the best sensitivity and specificity (75% and 68.9%, respectively) with a 2.4-fold risk of death (LR+ 2.4; 95% CI 1.6-3.7). Although hyperlactatemia was associated with severity and mortality in children 2 months to 5 years of age with pneumonia, its benefit was unclear.

Keywords

pediatrics, serum lactate, mortality, pneumonia, developing country

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Introduction

Pneumonia is globally the main cause of disease and death among children. Pneumonia (15%), along with diarrhea (8%), and malaria (5%) remain among the leading causes of death globally among children under age 5—accounting for almost a third of global under 5 deaths.[1] In 2016, pneumonia accounted for an estimated 650 000 deaths in infants and young children (<5 years) globally, the vast majority occurred in developing countries.[2] In Vietnam, pneumonia is the leading cause of pediatric hospital admission and places a huge burden on the health care system.[3]

Biomarkers signifying pneumonia severity and suggesting appropriate treatment may help reduce mortality; of these, lactate is a product of anaerobic cellular metabolism. It is used as an indicator of poor tissue oxygen delivery, and cell hypoxia to monitor critically ill children, including those with sepsis,[4] trauma,[5] acute respiratory distress syndrome,[6] and those with primary respiratory disease requiring extracorporeal membrane oxygenation (ECMO).[7] In developing countries, elevated serum lactate has been shown to appear in children with severe malaria,[8] kwashiorkor malnutrition,[9] severe anemia,[10] and pneumonia[11,12] as well.

This study aimed to determine whether serum lactate concentration measured at the time of hospital admission

[1]Hue University of Medicine and Pharmacy, Hue University, Hue City, Thua Thien Hue Province, Vietnam
[2]Binh Dinh General Hospital, Quy Nhon City, Binh Dinh Province, Vietnam
[3]Hue Central Hospital, Hue City, Thua Thien Hue Province, Vietnam

Corresponding Author:
Son Bui-Binh-Bao, Department of Pediatrics, Hue University of Medicine and Pharmacy, Hue University, 6 Ngo Quyen Street, Hue City, Thua Thien Hue Province 49000, Vietnam.
Emails: bbbson@hueuni.edu.vn; bbbson@huemed-univ.edu.vn

was a good predictor of mortality in children aged 2 months to 5 years with pneumonia.

Materials and Methods

We conducted a prospective cohort study of children aged 2 months to 5 years admitted to the Department of Pediatrics, Binh Dinh General Hospital, Quy Nhon City, Vietnam with WHO-defined pneumonia and severe pneumonia[13] between April 2019 and March 2020. Data recorded included age, gender, fever, respiratory physical signs, severity of pneumonia according to WHO criteria, treatment outcomes, arterial oxygen saturation measured by pulse oximetry (S_pO_2, %), white blood cell (WBC) count ($\times 10^9$/l), serum C-reactive protein (CRP) level (mg/l), and serum lactate concentration (mmol/l).

S_pO_2 was measured with a Mekics hand-held pulse oximeter model MP111 (Mekics Co., Ltd., Korea) on room air at admission. WBC count (10^9/l), including differential count, were routinely analyzed on enrollment with Sysmex XN-1000™ Hematology Analyzer (Japan). WBC count was presented as an absolute count and age-adjusted ratio, and neutrophils were presented as the percentage of the total WBC count. CRP was measured in serum samples by an automated turbidimetric assay and serum lactate concentration was analyzed using the AU480 Clinical Chemistry System (Beckman Coulter, Inc., USA). We defined hypoxemia as an arterial oxygen saturation measured by pulse oximetry of less than 90% when breathing air.[13] Hyperlactatemia was defined as serum lactate >2.0 mmol/l,[11] and was analyzed with the thresholds of >2.0 and >4.0 mmol/l. Serum CRP levels were evaluated with cut-off points of >10, >20, and >40 mg/l.

Univariate logistic regression was used to determine risk factors to mortality. The area under the receiver operating characteristics (ROC) curve was calculated for S_pO_2, WBC count, serum CRP level, and serum lactate concentration in prediction of mortality according to logistic regression. The association between lactate concentration and other clinical features was investigated using univariate logistic regression. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) 20.0.

Written informed consent was obtained from the patient's parent(s) or guardian(s). The study protocol was approved by the Ethics Committee at Hue University of Medicine and Pharmacy (H2019/279).

Results

Population

We enrolled 281 children aged 2 months to 5 years admitted with WHO-defined clinical pneumonia and severe pneumonia from April 2019 and March 2020. The proportion of pneumonia in children under 12 months of age was similar to that in children aged 12 months to 5 years (48.4% vs 51.6%, respectively); of which 26% of pneumonia occurred quite early before the age of 6 months. Pneumonia was more common in boys than in girls (60.1% vs 39.9%, respectively). Of these children, 43 (15.3%) were diagnosed as severe pneumonia. Among the 281 children, 8 died during their stay in hospital (case-death 2.8%), in which 7 deaths were children with severe pneumonia, and the other child with pneumonia. Mortality rates were not different between age groups; but different by gender, 6 (75%) deaths were in boys. Table 1 describes the patient clinical and laboratory characteristics in relation to treatment outcomes.

Many signs discriminated significantly between survivors and non-survivors in our study. The proportion of $S_pO_2 < 90\%$ was 87.5% among children who died and 9.2% among children who survived (OR = 69.4; 95% CI 8.2-587.4). Decreased conscious level/coma was observed in 50% of died children compared to in 1.8% of survived children (OR = 53.6), while a higher proportion of pneumonia children with diminished breath sounds died compared to pneumonia children without this sign on auscultation (62.5% vs 5.1%, respectively, OR = 30.8). The rates of other signs such as grunting and severe chest indrawing were also significantly higher in pneumonia children who died than in survivors (25.0% vs 1.5%, OR = 22.4; and 25.0% vs 2.2%, OR = 14.8%, respectively).

The proportions of peripheral leukocytosis and neutrophilic leukocytosis were not statistically different in pneumonia children who died, compared with those who survived (65.6% vs 50.0% and 39.9% vs 50.0%, respectively, $P > .05$ for all comparisons).

About 23.1% of children had a CRP concentration >20 mg/l, and 11.4% of children had a CRP concentration >40 mg/l. About 62.5% of children who died has a CRP concentration >20 mg/l (compared with 22.0% of those who survived), and 50% of died children has a CRP concentration >40 mg/l (compared with 10.3% of survivors). Serum CRP levels >20 and >40 mg/l increased the risk of death by 5.9 times (OR = 5.9; 95% CI 1.4-25.5) and by 8.8 times (OR = 8.8; 95% CI 2.1-36.9), respectively. About 94.7% of pneumonia children had a serum lactate concentration >2 mmol/l, while 33.8% of pneumonia children had a serum lactate concentration >4 mmol/l. All 8 deaths (100%) had a serum lactate concentration >2 mmol/l; and there were 6 deaths (75%) had a serum lactate concentration >4 mmol/l; and serum lactate concentrations >4 mmol/l increased the risk of death by 6.2 times (OR = 6.2; 95% CI 1.2-31.3).

Table 1. Clinical and Laboratory Features in Relation to Treatment Outcomes.

Characteristic	Entire cohort (n = 281)	Survivors (n = 273)	Non-survivors (n = 8)	*P*	OR
Age group (months)					
2-5	73 (26.0)	70 (25.6)	3 (37.5)	>.05	
6-11	63 (22.4)	61 (22.3)	2 (25.0)		
12-60	145 (51.6)	142 (52.0)	3 (37.5)		
Gender					
Boy	169 (60.1)	163 (59.7)	6 (75.0)	>.05[a]	
Girl	112 (39.9)	110 (40.3)	2 (25.0)		
Clinical examination					
Decreased conscious level/coma	9 (3.2)	5 (1.8)	4 (50.0)	<.05[a]	53.6 (10.4-277.5)
$S_pO_2 < 90\%$	32 (11.4)	25 (9.2)	7 (87.5)	<.05[a]	69.4 (8.2-587.4)
Grunting	6 (2.1)	4 (1.5)	2 (25.0)	<.05[a]	22.4 (3.4-147.0)
Severe chest indrawing	8 (2.8)	6 (2.2)	2 (25.0)	<.05[a]	14.8 (2.5-89.1)
Diminished breath sounds	19 (6.8)	14 (5.1)	5 (62.5)	<.05[a]	30.8 (6.7-142.3)
Peripheral leukocyte count					
Leukocytosis	183 (65.1)	179 (65.6)	4 (50.0)	>.05[a]	
Neutrophilic leukocytosis	113 (40.2)	109 (39.9)	4 (50.0)	>.05[a]	
Serum CRP level (mg/l)					
>20	65 (23.1)	60 (22.0)	5 (62.5)	<.05[a]	5.9 (1.4-25.5)
>40	32 (11.4)	28 (10.3)	4 (50.0)	<.05[a]	8.8 (2.1-36.9)
Serum lactate concentration (mmol/l)					
>2	266 (94.7)	258 (94.5)	8 (100)		
>4	95 (33.8)	89 (32.6)	6 (75.0)	<.05[a]	6.2 (1.2-31.3)
Pneumonia severity					
Pneumonia	238 (84.7)	237 (86.8)	1 (12.5)	<.05	46.1 (5.5-385.6)
Severe pneumonia	43 (15.3)	36 (13.2)	7 (87.5)		

Abbreviations: CRP, C-reactive protein; S_pO_2, arterial oxygen saturation measured by pulse oximetry.
[a]Fisher's exact test.

Factors Associated With Serum Lactate

Table 2 indicates the serum lactate concentrations in relation to age groups, gender, clinical characteristics and treatment outcomes. The median serum lactate concentration for entire pneumonia children in this study was 3.6 mmol/l (IQR 2.8-4.3); 3.6 mmol/l (IQR 2.9-4.4) in boys; and 3.4 mmol/l (IQR 2.7-4.1) in girls ($P < .05$). The median lactate concentrations were not significantly different between age groups. The median lactate concentration was 4.8 mmol/l (IQR 2.6-6.9) among children who died and 3.6 mmol/l (IQR 2.8-4.3) among children who survived ($P > .05$); 4.1 mmol/l (IQR 2.7-4.7) among children with severe pneumonia and 3.5 mmol/l (IQR 2.8-4.3) among children with pneumonia ($P > .05$).

Higher concentrations of lactate were also found in children with unable to feed/drink compared to children with normal feed/drink (median 6.5, IQR 3.9-9.4, compared to 3.6, IQR 2.8-4.3 mmol/l); in children with decreased conscious level compared to children with normal conscious state (median 4.6, IQR 4.1-8.2, compared to 3.5, IQR 2.8-4.3 mmol/l); and in those with diminished breath sounds compare to those with normal breath sounds (median 4.2, IQR 3.6-6.9, compared to 3.5, IQR 2.8-5.0 mmol/l, $P < .05$ for all comparisons).

The results, as shown in Table 3, indicate that the serum lactate concentration had a moderate negative correlation with S_pO_2 (r_s: −0.30 [−0.46 to −0.09]), a moderate positive correlation with WBC count (r_s: 0.30 [0.14-0.45]) and a low positive correlation with serum CRP level (r_s: 0.28 [0.14-0.43]).

Discriminative Power of S_pO_2, WBC Count, Serum CRP Level, and Serum Lactate Concentration as Predictors of Mortality

As Table 4 shows, the WBC count, serum CRP level, and serum lactate concentration were not specific in predicting pneumonia-related mortality (AUC 0.55, 95% CI 0.49-0.61; AUC 0.66, 95% CI 0.60-0.71; and AUC 0.68, 95% CI 0.62-0.73, respectively). Serum lactate concentration cut-off of >4.06 mmol/l had the best sensitivity and specificity (75% and 68.9%, respectively)

Table 2. Population, Clinical Features and Treatment Outcomes Associated With Serum Lactate.

Characteristic	Entire cohort (n = 281)	Serum lactate concentration (mmol/l) median (25th-75th)	*P*
Entire population	281	3.6 (2.8-4.3)	
Age group (months)			
2-5	73	3.6 (2.9-4.3)	>.05
6-11	63	3.5 (3.1-4.2)	
12-60	145	3.6 (2.6-4.5)	
Gender			
Boy	169	3.6 (2.9-4.4)	<.05
Girl	112	3.4 (2.7-4.1)	
Clinical features			
Convulsions			
Yes	6	4.7 (2.0-9.4)	>.05
No	275	3.6 (2.8-4.3)	
Unable to feed/drink			
Yes	7	6.5 (3.9-9.4)	<.05
No	274	3.6 (2.8-4.3)	
Decreased conscious level/coma			
Yes	9	4.6 (4.1-8.2)	<.05
No	272	3.5 (2.8-4.3)	
Fever			
Yes	196	3.6 (2.7-4.4)	>.05
No	85	3.6 (3.0-4.3)	
Grunting			
Yes	6	4.3 (2.6-5.1)	>.05
No	275	3.6 (2.8-4.3)	
Severe chest indrawing			
Yes	8	3.0 (2.5-6.7)	>.05
No	273	3.6 (2.8-4.3)	
Diminished breath sounds			
Yes	19	4.2 (3.6-6.9)	<.05
No	262	3.5 (2.8-5.0)	
Crackles			
Yes	276	3.6 (2.8-4.3)	>.05
No	5	3.1 (2.5-6.3)	
S_pO_2 (%)			
<90	32	4.1 (2.7-5.5)	<.05
≥90	249	3.5 (2.8-4.3)	
Pneumonia severity			
Pneumonia	238	3.5 (2.8-4.3)	>.05
Severe pneumonia	43	4.1 (2.7-4.7)	
Treatment outcomes			
Survivors	273	3.6 (2.8-4.3)	>.05
Non-survivors	8	4.8 (2.6-6.9)	

Abbreviations: S_pO_2, arterial oxygen saturation measured by pulse oximetry.

with a 2.4-fold risk of death (LR+ 2.4; 95% CI 1.6-3.7). Among the predictors of mortality, S_pO_2, a noninvasive assessment, discriminated best between survivors and non-survivors in our study with AUC 0.96 and 95% CI 0.94 to 0.98. Oxygen saturation of ≤86% accurately predicted death with high sensitivity and specificity (87.5% and 95.2%, respectively); LR+ 18.4 (95% CI 10.2-33.2); and LR− 0.1 (95% CI 0.02-0.8).

Discussion

This study showed that serum lactate concentration was associated with many clinical signs, changes in

Table 3. S_pO_2, WBC Count, and Serum CRP Level in Relation to Serum Lactate Concentration.

Characteristic	Serum lactate concentration (mmol/l)	
	r_s	*P*
S_pO_2	−0.30 (−0.46 to −0.09)	<.05
WBC count	0.30 (0.14 to 0.45)	<.05
Serum CRP level	0.28 (0.14 to 0.43)	<.05

Abbreviations: CRP, C-reactive protein; r_s, Spearman's rank correlation coefficient; S_pO_2, arterial oxygen saturation measured by pulse oximetry; WBC, white blood cell.

Table 4. Discriminative Power of S_pO_2, WBC, CRP, and Lactate as Predictors of Mortality.

Predictors	AUC (95% CI)	Cut-off	Sensitivity	Specificity	LR+	LR−
S_pO_2	0.96 (0.94-0.98)	≤86%	87.5	95.2	18.4 (10.2-33.2)	0.1 (0.02-0.8)
WBC count	0.55 (0.49-0.61)	≤10 130/mm^3	62.5	60.8	1.6 (0.9-2.8)	0.6 (0.3-1.5)
Serum CRP level	0.66 (0.60-0.71)	>27.8 mg/l	62.5	86.5	4.6 (2.5-8.5)	0.4 (0.2-1.1)
Serum lactate concentration	0.68 (0.62-0.73)	>4.06 mmol/l	75.0	68.9	2.4 (1.6-3.7)	0.4 (0.1-1.2)

Abbreviations: AUC, area under ROC curve; CI, confidence interval; CRP, C-reactive protein; LR−, negative likelihood ratio; LR+, positive likelihood ratio; S_pO_2, arterial oxygen saturation measured by pulse oximetry; WBC, white blood cell.

peripheral white blood cell counts and serum CRP level, as well, in pneumonia in children aged 2 months to 5 years. Children with signs of serious illness such as grunting, severe chest indrawing; and especially those unable to feed/drink, those with decreased conscious level or coma, had significantly higher serum lactate concentration. These signs have also been shown by previous studies to be related to hypoxemia.[14] Therefore, serum lactate concentration was higher in the severe pneumonia group than in the pneumonia group.

Some studies in adults have demonstrated that initial serum lactate level on admission was associated with mortality in patients with pneumonia.[15,16] Other studies in children have also demonstrated that hyperlactatemia can be used as an indicator of poor prognosis in critically ill children in the Pediatric Intensive Care Units (PICUs); therein, initial serum lactate levels >2 mmol/l were observed in the majority of patients admitted to the PICUs,[4,7,17-19] and lactate levels >5[17,18] or >5.55 mmol/l[19] had high sensitivity and specificity in predicting mortality. Our study also recorded that 75% of children with pneumonia who died had serum lactate level >4 mmol/l and this lactate threshold increased the risk of mortality more than 6 times (OR=6.2; 95% CI 1.2-31.3). However, based on ROC analysis, lactate level had only a low predictive value for mortality risk in children aged 2 months to 5 years with pneumonia (AUC=0.68; 95% CI 0.62-0.73). This value was not similar to the results of other authors.[11] Serum lactate level >4.06 mmol/l was also noted the cut-off point with the best sensitivity and specificity (though not high) in predicting mortality (75.0% and 68.9%, respectively).

Meanwhile, oxygen saturation had a very good predictive value of mortality (AUC=0.96; 95% CI 0.94-0.98); and S_pO_2 threshold ≤86% had very high sensitivity and specificity (87.5% and 95.2% respectively) in predicting mortality. Among 8 deaths in our study, 87.5% (7/8 patients) had S_pO_2 < 90%; and this cut-off was defined as high risk of death with OR=69.4; 95% CI 8.2 to 587.4. This was also mentioned by some previous studies; when hypoxemia was found to be a stronger predictor of mortality. A recent study in Malawi showed that S_pO_2 < 90% was an independent predictor of death from WHO danger signs with RR=9.37; 95% CI 2.17 to 40.4.[20]

Hypoxemia is common in pneumonia due to ventilation-perfusion mismatch that results in reducing oxygen exchange and creating pulmonary shunts. Additionally, there may be a decrease in minute hypoventilation in serious condition or in late stage. Hypoxemia represents the severity of pneumonia, so the prognostic value of this factor is very high. One question to be raised is whether serum lactate concentration can reflect blood oxygenation status. Historically, lactate concentration was considered a "waste product" of anaerobic metabolism. When oxygen supply to the tissues is insufficient to sustain aerobic metabolism, cells must rely on anaerobic metabolism, a form of energy-producing process that does not require oxygen, but produces lactic acid as a secondary product. The more severe the lactic acidosis suggests the more critical the condition; and is considered an important indicator of tissue hypoperfusion in shock and hypoxemia. This raised the issue of quantifying and monitoring lactate levels in critically ill patients

in general as well as in patients with shock or pneumonia, in particular.[21] However, more recent evidence has suggested other ways of understanding the mechanisms of lactate formation in the body; through which an increase in serum lactate level is complex and not necessarily related to hypoxemia.[22] In addition to the lactate formation mechanism mentioned, it is also important to consider the mechanism of lactate production by well-oxygenated tissues. In muscle, bone, and some other tissues, aerobic glycolysis involves supplying ATP to the Na-K-ATPase pump, and its activity is stimulated by epinephrine. In traumatic patients, increased Na-K-ATPase activity may be observed; reflected by hypokalemia. The hyperlactatemia in these cases reflects increased aerobic glycolysis in muscle and bone secondary to epinephrine-stimulated Na-K-ATPase activity rather than hypoperfusion-induced anaerobic glycolysis.[23] Besides, this aerobic glycolysis process is also an important mechanism for the generation of more ATP under stress.[24] The result of our study also recognized this when serum lactate concentration had a weak correlation ($r_s = -0.3$) with pulse oximetry, a valuable indicator of blood oxygenation status.

Ramakrishna et al in a study in children with WHO-defined pneumonia in Malawi noted that 65 out of 87 children with hypoxemia by definition ($S_pO_2 < 90\%$) had normal lactate concentrations. The authors concluded that elevated serum lactate concentration should be used in conjunction with known risk factors, young age, and hypoxemia in identifying the sickest patients.[11] Some other studies have suggested that hyperlactatemia may predict mortality if it persisted after 24 hours of treatment[4]; and serum lactate level in the first 24 hours of admission had the best sensitivity and specificity in predicting outcome.[25]

Inflammatory markers such as CRP, IL-6, IL-8, and procalcitonin levels have also been shown to be potential to predict severe community-acquired pneumonia in pediatric populations.[26] However, in our study, serum CRP levels, similar to serum lactate levels, had a low value (AUC = 0.66; 95% CI 0.60-0.71) in predicting mortality in children with pneumonia. Therefore, we suggest that serum lactate level should be combined with clinical manifestations and non-invasive but high-value indicators such as S_pO_2 in approaching, assessing, and prognosing children with pneumonia.

Conclusion

Serum lactate has been widely evaluated in pediatric clinical practice. Although there was an association between hyperlactatemia and severity as well as mortality in children aged 2 months to 5 years with pneumonia but its benefit was unclear. Future studies are needed to investigate the role of serum lactate as a biomarker in pneumonia for better treatment and prognosis.

Declaration of Conflicting Interests

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ORCID iDs

Son Bui-Binh-Bao https://orcid.org/0000-0002-7373-8300
Nguyen Thi Kim Hoa https://orcid.org/0000-0003-2525-4368

References

1. United Nations Children's Fund. United Nations Inter-Agency Group for Child Mortality Estimation (UN IGME). Levels & Trends in Child Mortality – Report 2019. United Nations Children's Fund; 2019.
2. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease study 2016. *Lancet Infect Dis*. 2018;18(11):1191-1210. doi:10.1016/S1473-3099(18)30310-4
3. Nguyen TKP, Nguyen DV, Truong TNH, Tran MD, Graham SM, Marais BJ. Disease spectrum and management of children admitted with acute respiratory infection in Viet Nam. *Trop Med Int Health*. 2017;22(6):688-695. doi:10.1111/tmi.12874
4. Hatherill M, McIntyre AG, Wattie M, Murdoch IA. Early hyperlactataemia in critically ill children. *Intensive Care Med*. 2000;26(3):314-318. doi:10.1007/s001340051155
5. Lawton L, Crouch R, Voegeli D. Is lactate an effective clinical marker of outcome for children with major trauma? A literature review. *Int Emerg Nurs*. 2016;28:39-45. doi:10.1016/j.ienj.2016.04.002
6. Davis SL, Furman DP, Costarino AT Jr. Adult respiratory distress syndrome in children: associated disease, clinical course, and predictors of death. *J Pediatr*. 1993;123(1):35-45. doi:10.1016/s0022-3476(05)81534-3
7. Buijs EA, Houmes RJ, Rizopoulos D, Wildschut ED, Reiss IK, Ince C, et al. Arterial lactate for predicting mortality in children requiring extracorporeal membrane oxygenation. *Minerva Anestesiol*. 2014;80(12):1282-1293.
8. Mockenhaupt FP, Ehrhardt S, Burkhardt J, et al. Manifestation and outcome of severe malaria in children in northern Ghana. *Am J Trop Med Hyg*. 2004;71(2):167-172.
9. Whitehead RG, Harland PS. Blood glucose, lactate and pyruvate in kwashiorkor. *Br J Nutr*. 1966;20(4):825-831. doi:10.1079/bjn19660085

10. English M, Muambi B, Mithwani S, Marsh K. Lactic acidosis and oxygen debt in African children with severe anaemia. *QJM*. 1997;90(9):563-569. doi:10.1093/qjmed/90.9.563
11. Ramakrishna B, Graham SM, Phiri A, Mankhambo L, Duke T. Lactate as a predictor of mortality in Malawian children with WHO-defined pneumonia. *Arch Dis Child*. 2012;97(4):336-342. doi:10.1136/archdischild-2011-300920
12. Ma C, Gunaratnam LC, Ericson A, et al. Handheld point-of-care lactate measurement at admission predicts mortality in Ugandan children hospitalized with pneumonia: a prospective cohort study. *Am J Trop Med Hyg*. 2019;100(1):37-42. doi:10.4269/ajtmh.18-0344
13. World Health Organization. Pneumonia. In: *WHO Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses*, 2nd ed. World Health Organization; 2013:80-87.
14. Basnet S, Adhikari RK, Gurung CK. Hypoxemia in children with pneumonia and its clinical predictors. *Indian J Pediatr*. 2006;73(9):777-781. doi:10.1007/BF02790384
15. Gwak MH, Jo S, Jeong T, et al. Initial serum lactate level is associated with inpatient mortality in patients with community-acquired pneumonia. *Am J Emerg Med*. 2015;33(5):685-690. doi:10.1016/j.ajem.2015.03.002
16. Jo S, Jeong T, Lee JB, Jin Y, Yoon J, Park B. Validation of modified early warning score using serum lactate level in community-acquired pneumonia patients. The national early warning score–lactate score. *Am J Emerg Med*. 2016;34(3):536-541. doi:10.1016/j.ajem.2015.12.067
17. Jat KR, Jhamb U, Gupta VK. Serum lactate levels as the predictor of outcome in pediatric septic shock. *Indian J Crit Care Med*. 2011;15(2):102-107. doi:10.4103/0972-5229.83017
18. Kim YA, Ha EJ, Jhang WK, Park SJ. Early blood lactate area as a prognostic marker in pediatric septic shock. *Intensive Care Med*. 2013;39(10):1818-1823. doi:10.1007/s00134-013-2959-z
19. Bai Z, Zhu X, Li M, et al. Effectiveness of predicting in-hospital mortality in critically ill children by assessing blood lactate levels at admission. *BMC Pediatr*. 2014;14:83. doi:10.1186/1471-2431-14-83
20. Colbourn T, King C, Beard J, et al. Predictive value of pulse oximetry for mortality in infants and children presenting to primary care with clinical pneumonia in rural Malawi: a data linkage study. *PLoS Med*. 2020;17(10):e1003300. doi:10.1371/journal.pmed.1003300
21. Liu W, Peng L, Hua S. Clinical significance of dynamic monitoring of blood lactic acid, oxygenation index and C-reactive protein levels in patients with severe pneumonia. *Exp Ther Med*. 2015;10(5):1824-1828. doi:10.3892/etm.2015.2770
22. Fine-Goulden MR, Durward A. How to use lactate. *Arch Dis Child Educ Pract Ed*. 2014;99(1):17-22. doi:10.1136/archdischild-2013-304338
23. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet*. 1999;354(9177):505-508. doi:10.1016/S0140-6736(98)91132-1
24. Kushimoto S, Akaishi S, Sato T, et al. Lactate, a useful marker for disease mortality and severity but an unreliable marker of tissue hypoxia/hypoperfusion in critically ill patients. *Acute Med Surg*. 2016;3(4):293-297. doi:10.1002/ams2.207
25. Shalaby A, Khalafallah O, Galal M, Assal HH, Ahmed N. Correlation between serum lactate and other oxygenation indices as a predictor of outcome in respiratory ICU patients. *Egypt J Chest Dis Tuberc*. 2016;65(3):695-700. doi:10.1016/j.ejcdt.2016.04.010
26. Fernandes CD, Arriaga MB, Costa MCM, et al. Host inflammatory biomarkers of disease severity in pediatric community-acquired pneumonia: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2019;6(12):ofz520. doi:10.1093/ofid/ofz520